



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Interim Guidance on Tolerance Expressions

FROM: Steve Knizner, Associate Division Director
Health Effects Division (7509C)

TO: HED Staff

This document is intended to provide guidance to HED staff who are involved in the preparation of tolerance expressions for pesticide residues whether in the context of establishing tolerances for new pesticides, establishing additional tolerances for currently-registered pesticides, or re-examining existing tolerances in registration review. When working on establishing additional tolerances for currently-registered pesticides, HED staff will need to consult with OGC in determining whether any of the recommended changes below can be incorporated into the tolerance expressions for pre-existing tolerances. At this time the guidance is being designated as "interim" due to the fact that FDA and USDA staff involved with residue monitoring and enforcement have not had the opportunity to comment on it.

Establishment of FFDCA tolerances in conjunction with registration of a pesticide use under FIFRA is critical in ensuring that legal uses of a pesticide under FIFRA do not result in illegal pesticide residues in food under the FFDCA. The basic scheme under the FFDCA provides that a pesticide residue in food renders the food adulterated unless there is a tolerance in place for that pesticide residue and the level of residue is within the tolerance. Importantly, the FFDCA defines a pesticide residue as including metabolites and degradates of the pesticide. Accordingly, unless a pesticide's metabolites and degradates are properly addressed in the tolerance, legal use of a pesticide might result in adulterated food.

In evaluating whether a pesticide metabolite or degradate in a food renders the food adulterated, enforcement agencies face two questions: (1) is the metabolite/degradate covered by the applicable tolerance for the parent pesticide? and (2) if so, how should it be determined whether the level of parent and metabolite exceed the tolerance value? The first question speaks to the scope or "coverage" of the tolerance while the second question addresses "measurement" of residues. Language was added to FFDCA Section 408 by the FQPA which addresses these

questions. A complete copy of that text from section 408(a)(3) is included at the end of this document.

The FQPA-added language states that a tolerance for a pesticide covers pesticide metabolites and degradates not mentioned in the tolerance *unless, among other things, the tolerance explicitly states it applies to the parent only or specifically excludes a metabolite or degradate*. The new provision also establishes that, in determining whether any combination of detected residues of parent and unmentioned metabolite comply with the tolerance level, the level of the unmentioned metabolite is to be converted to the stoichiometrically equivalent level of the parent and then combined with the level of parent residues.

In the past, drafting of tolerance expressions has focused more on the measurement issue than the question of coverage. Thus, tolerance expressions tend to be a single sentence (1) stating that a tolerance is established for the residues of a given pesticide and (2) specifying the precise chemical substances that are to be measured by the analytic enforcement method. The tolerance would then specify tolerance levels for various commodities with those levels based on the amount of the specific named substances found in field trials. For example, the tolerance for coumaphos reads:

Tolerances for residues of the insecticide **coumaphos** (O,O -diethyl O -3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl phosphorothioate and its oxygen analog (O,O -diethyl O -3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl phosphate) in or on food commodities as follows: cattle, fat – 1 ppm, etc. . . . (40 CFR 180.189)

The new language in FFDCA section 408(a)(3) helps with the coverage issue with tolerances such as this but complicates the measurement question. The coverage issue is addressed because section 408(a)(3) would dictate that coumaphos metabolites and degradates not named in the tolerance are nonetheless covered by the tolerance because they have not been expressly excluded. Measurement is potentially a problem, however, because section 408(a)(3) essentially specifies that any unnamed metabolites or degradates that are detected should be summed (once converted) with the substances named in the tolerance expression in determining compliance with the tolerance levels. If a significant metabolite (whether of toxicological concern or not) has not been included in the tolerance expression, the mandate of section 408(a)(3) might result in a finding of over-tolerance residues even though that was not OPP's intent.

Prior drafting practice also may result in coverage problems in some instances. In contrast to the approach taken with the coumaphos tolerance above, a few tolerances appear to limit coverage to the parent pesticide or to exclude certain metabolites. Use of terms such as “per se” following mention of a particular substance in a tolerance expression may be interpreted under section 408(a)(3) as limiting the coverage of the tolerance to the specified substance only thus rendering the food adulterated if any metabolite or degradate is detected (and there is not otherwise a tolerance for that metabolite or degradate). The spirodiclofen tolerance provides an example:

Tolerances are established for residues of spirodiclofen **per se** (3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4.5]dec-3-en-4-yl 2,2-dimethylbutanoate) in or on the following plant commodities . . . (40 CFR 608).

To address these "coverage" and "measurement" issues, this guidance has the following recommendations for the drafting of tolerance expressions:

1. A tolerance expression should explicitly address both the coverage and measurement. Preferably, this should be done in two separate sentences with the first sentence describing the coverage of the tolerance and the second specifying the substances to be measured in determining compliance with the tolerance levels.
2. The Coverage Sentence. In general, the coverage sentence should be drafted so as to explicitly cover the pesticide parent as well as all metabolites and degradates. As a model, this guidance recommends the following: *Tolerances are established for residues of [pesticide name], including its metabolites and degradates, in or on the commodities in the table below.* Further, it is recommended that drafters no longer use the term "*per se*" or similar language in tolerance expressions unless there is some other tolerance established to address the metabolites and degradates excluded by such language.
3. The Measurement Sentence. The measurement sentence should specify the exact residues to be measured and compared to the numerical tolerance levels for each commodity. The term "only" should be used to describe these residues to emphasize that no other residues are to be included in the measured amount, which then is compared to the tolerance level to determine compliance with the tolerance level. A model measurement sentence is as follows: *Compliance with the tolerance levels specified below is to be determined by measuring only [specify precise chemical substances to be measured by the analytic method].* In those cases where one of the measured residues is calculated or expressed in terms of the molecular weight of the parent pesticide, the terminology should include the terminology "stoichiometric equivalent" to mirror the language in FFDCA.

To aid reviewers in this process, examples are shown below of typical situations that are encountered for tolerance expressions. In the case of chemicals that are presented to the HED Residues of Concern Knowledge-Based Subcommittee (ROCKS), the ROCKS report will provide the recommended tolerance language.

EXAMPLES OF TOLERANCE EXPRESSIONS

Generic Boilerplate

Tolerances are established for residues of [pesticide name], including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only [specify precise chemical substances to be measured by the analytic method].

Enforcement Method and Risk Assessment includes Parent, Only

Tolerances are established for residues of fenpropidin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only fenpropidin (1-[3-[4-(1,1-dimethylethyl)phenyl]-2-methylpropyl]piperidine).

Enforcement Method is for Parent Only, but Risk Assessment Includes Metabolites

Note that the first example below addresses the case where the parent pesticide is measured as the sum of multiple isomers, while the second example does not have isomers that are individually determined.

Metconazole; tolerances for residues

(a) General. Tolerances are established for residues of metconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only metconazole, (5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl) cyclopentanol), as the sum of its cis- and trans-isomers in or on the commodity.

Buprofezin; tolerances for residues

(a) General. Tolerances are established for residues of buprofezin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only buprofezin, 2-[(1,1-dimethylethyl)imino]tetrahydro-3(1-methylethyl)-5-phenyl-4 H -1,3,5-thiadiazin-4-one, in or on the commodity.

Multiple Analytes Summed to Determine Tolerance Level

Oxamyl; tolerances for residues

(a) General. Tolerances are established for residues of the insecticide oxamyl, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of oxamyl (methyl N,N -dimethyl- N -[(methylcarbamoyl)-oxy]-1-thiooxamimidate) and its oxime metabolite (methyl N,N-dimethyl-N-hydroxy-1-thiooxamimidate), calculated as the stoichiometric equivalent of oxamyl, in or on the commodity.

Multiple Residues Converted to One Analyte (“Common Moiety”)

Acibenzolar; tolerances for residues

(a) General. Tolerances are established for residues of acibenzolar-S-methyl [benzo(1,2,3)thiadiazole-7-carbothioic acid-S-methyl ester], including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only those acibenzolar-S-methyl residues

convertible to benzo(1,2,3)thiadiazole-7-carboxylic acid (CGA-210007), expressed as the stoichiometric equivalent of acibenzolar-S-methyl, in or on the commodity.

Metabolite is also a Pesticide Active Ingredient

The following are possible ways to express tolerances when one pesticide (e.g., thiamethoxam) metabolizes to another pesticide (e.g., clothianidin). These examples follow the latest approach used for acephate and methamidophos in that the section for the pesticidal metabolite has separate sections to address whether the residues arise from application of that substance or of the precursor pesticide.

180.xxx Thiamethoxam

Tolerances are established for residues of the insecticide thiamethoxam, including its metabolites and degradates other than clothianidin¹, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only thiamethoxam (...chemical name ...) in or on the commodity.

COMMODITY	PPM

¹Residues of the thiamethoxam metabolite, clothianidin, are regulated under 40 CFR 180.yyy.

180.yyy Clothianidin

(a) Tolerances are established for residues of the insecticide clothianidin, including its metabolites and degradates, in or on the commodities in the table below as a result of the application of clothianidin. Compliance with the tolerance levels specified below is to be determined by measuring only clothianidin (...chemical name ...) in or on the commodity.

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(b) Tolerances are established for residues of the insecticide clothianidin, including its metabolites and degradates, in or on the commodities in the table below as a result of the application of thiamethoxam. Compliance with the tolerance levels specified below is to be determined by measuring only clothianidin (...chemical name ...) in or on the commodity.

NOTE: A third section (c) could be added to address commodities on which both clothianidin and thiamethoxam are registered (i.e., "... as a result of application of clothianidin and/or thiamethoxam...").

TEXT ADDED TO FFDCA BY FQPA FOR TOLERANCES

SEC. 408(a) REQUIREMENT FOR TOLERANCE OR EXEMPTION

(3) RESIDUES OF DEGRADATION PRODUCTS

If a pesticide chemical residue is present in or on a food because it is a metabolite or other degradation product of a precursor substance that itself is a pesticide chemical or pesticide chemical residue, such a residue shall not be considered to be unsafe within the meaning of section 402(a)(2)(B) of this title despite the lack of a tolerance or exemption from the need for a tolerance for such residue in or on such food if—

(A) the Administrator has not determined that the degradation product is likely to pose any potential health risk from dietary exposure that is of a different type than, or of a greater significance than, any risk posed by dietary exposure to the precursor substance;

(B) either—

(i) a tolerance is in effect under this section for residues of the precursor substance in or on the food, and the combined level of residues of the degradation product and the precursor substance in or on the food is at or below the stoichiometrically equivalent level that would be permitted by the tolerance if the residue consisted only of the precursor substance rather than the degradation product; or

(ii) an exemption from the need for a tolerance is in effect under this section for residues of the precursor substance in or on the food; and

(C) the tolerance or exemption for residues of the precursor substance does not state that it applies only to particular named substances and does not state that it does not apply to residues of the degradation product.